Urologic Complications in Patients with Diabetes

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Introduction

Diabetes mellitus (DM) is a group of metabolic diseases associated with high glucose levels that cause systemic long-term damage, dysfunction, and failure of several tissues [2]. Among the consequences of this chronic hyperglycemic state, patients with DM suffer several urologic complications that involve endothelial and neural damage all along the genitourinary tract with significant economical and quality of life costs.

The worldwide incidence of urologic complications associated with DM is increasing because of the high incidence of obesity in the entire world [64]. The effect of obesity in our society is growing at a worrying rate, and it is associated with an increasing risk of non-insulin-dependent diabetes. Clinicians have the opportunity to prevent, diagnose, and change the evolution of these urologic complications among patients with diabetes by maintaining a proper weight [57].

Diabetes has been associated with an earlier presentation and increased severity of urologic complications [46]. DM leads to nerve function disturbance, loss of innervation of neuromuscular nerve terminals, abnormal immune response, and altered sympathetic/parasympathetic innervation [13]. Therefore, peripheral accumulations of fat in the abdominal region of patients with diabetes have been associated with an increased risk of urologic complications such as urinary incontinence, erectile dysfunction, benign prostatic hyperplasia, and urinary tract infections and possibly with cancer [57].

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Lower Urinary Tract Dysfunction

Bladder Dysfunction (BD) and Cystopathy

Some bladder symptoms occurring in patients with DM are known as diabetic bladder dysfunction or diabetic cystopathy, which include lower urinary tract symptoms (LUTS), and are characterized by increased post-voiding residual volume due to inadequate bladder emptying, causing an increased bladder capacity, worsened by reduced bladder sensation and contraction [34].

Almost half of patients with DM suffer from different degrees of BD (74% men and 59.26% women), which causes an increased post-void residual urine and urinary incontinence, causing infections, bladder stones, or eventually kidney damage [47]. In men, bladder disorders are worsened by the age-associated increase in prostate volume.

Obese and diabetic women are expected to have more pelvic floor disorders, such as stress urinary incontinence and overactive bladder [46] which could be related to increased abdominal pressure by the abdominal panniculus exerting unwanted pressure on the pelvic organs, uterus, bladder, urethral sphincters, and vagina [57], peripheral neuropathy, and loss of bladder support. Insulin treatment of women with DM increases the risk of urge incontinence, in comparison with women treated with metformin, which does not have any effect on incontinence [11, 45].

Bladder hypersensitivity is reported as the most frequent finding, ranging from 39% to 61% in DM patients in numerous clinical studies [34]. Even more, an important predictor of bladder dysfunction is the presence of peripheral neuropathy, nephropathy, and the association of metabolic syndrome [46].

Pathophysiology

During the early stages of diabetic cystopathy, there is an increase in bladder storage capacity, which affects its compliance or ability to adapt to the building pressure as the bladder fills [51]. Several mechanisms that induce abnormalities in bladder function have been described at the level of the detru-

J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-030-11815-0_55

sor muscle, including changes in intracellular connections and excitability, density of muscarinic receptors, genetic traits, and changes in intracellular signaling (Zhengyong et al. 2015). All of these contributing factors result in diminished contractility and increase of the post-void residual volume. Compensatory bladder hypertrophy causes further bladder instability that diminishes its contraction strength because of collagen deposits, making tightening of the detrusor muscle ineffective [51]. Another theory is the associated increase in diuresis due to the hyperglycemic status resulting in neural and endothelial damage, which can collectively lead to hypertrophy of the detrusor muscle in an attempt to adapt to these changes. On the other hand, abnormalities in the calcium and potassium cellular wall channels increase the activity of the detrusor muscle and further overactivity [20]. In addition, rabbit models have shown that aldose reductase overexpression and increase in lipid peroxidation products result in diminished detrusor contractility [16].

Another issue influencing bladder hypertrophy could be an increase in oxidative stress, associated with further damage to the bladder muscles [65] or induced by an axonal transport deficiency of neural growth factor (NGF). Bladder tissue remodeling is also associated with downregulation of tissue growth factor (TGF) and collagen mRNA levels, which induce an increase in elastin synthesis. These factors may result in an increase in bladder compliance in patients with diabetes associated with reduction in collagen synthesis [38].

Neuronal control of bladder function consists of an interaction between autonomic sympathetic and parasympathetic, and somatic afferent and efferent pathways. Patients with diabetic cystopathy present somatic and autonomic neuropathy. Furthermore, cells under long periods of exposure to hyperglycemia undergo accumulation of oxidative stress products, causing axonal degeneration and nerve damage, decreasing nerve conduction, and triggering diabetic cystopathy and erectile dysfunction [7]. In addition, decreased sensation of bladder filling, produced by nerve damage, may cause over-distention and further hypocontractility of the bladder wall in diabetic patients. Diabetic cystopathy also involves neuropathic changes, produced by hyperexcitability of urethral afferent reflex, leading to dysfunction of the external urethral sphincter and reducing urethral smooth muscle relaxation with obstruction to the outflow of urine.

Long-standing diabetes also affects the peristaltic function of the ureters by interfering with ureteral muscle cells and nerve function, causing upper urinary tract dysfunction, urine stasis, and eventually formation of kidney stones [13]. The micturition reflex is a neural stimulus controlled by M2 and M3 receptors. Patients with diabetes have higher numbers of muscarinic receptors in the urothelium which increase the sensory nerve activity, modifying the detrusor contraction, causing further bladder dysfunction and urine stasis [20].

Clinical Manifestations

In the early stages of diabetic bladder, compensatory changes maintain the capacity to sustain a normal dieresis. In later stages, decreased micturition pressure and increasing urethral obstruction lead to larger volumes of post-void residual urine, producing a wide variety of symptoms which vary from urge micturition and incontinence (a sensation of imminent urine outflow) (risk of 40–80%) to the most severe expression of overflow incontinence (in which the bladder empties because of excessive residual urine without the patient's control) [12]. Diabetic patients complain of lower urinary tract symptoms, including urgency; difficulties to begin, maintain, and finish micturition; inadequate emptying or sensation of residual urine; frequent micturitions during the day- and nighttime; and slow or diminished urine flow of different levels of severity. Consequently, voiding reflexes seem to be diminished or inactive causing progressive asymptomatic increase in bladder capacity, which can eventually cause urinary retention, bladder stone formation, diverticula, infection, upper urinary tract dilation, and kidney damage. In contrast, diabetic bladder dysfunction can also present as overactive bladder syndrome with the corresponding frequent bladder emptying during the day- and at nighttime, urgency, and lower urinary tract symptoms. Hypersensitivity and hypercontractility of the bladder are more common than hypocontractility [34].

Diabetic cystopathy and bladder dysfunction are common in long-standing diabetic patients. They could be asymptomatic or manifest a broad spectrum of clinical symptoms, ranging from voiding complaints due to overactive bladder and urge incontinence due to decreased bladder sensation to overflow incontinence and acute urinary retention [46]. Bladder symptoms can be divided into irritative and obstructive. Irritative symptoms involve overexcited detrusor muscle, causing urgency, pollakiuria, nocturia, and urgency incontinence, known as overactive bladder syndrome. Obstructive symptoms include decreased size and strength of the voiding flow, terminal dribbling, decreased sensation of a full bladder, and high post-void residual urine. Obstructive symptoms are related to a pseudo-obstructive bladder, represent the last phase of visceral diabetic neuropathy, and are associated with low urine flow that can be demonstrated with uroflowmetry, high post-mictional residue, and urodynamic studies, which show an hypotonic bladder in the cystometry caused by a myogenic alteration of the neuronal and microvasculature [23, 51].

Diagnosis

The study approach of diabetic cystopathy depends on individual patient symptoms, severity, renal function, and impact on quality of life. In patients with symptoms of bladder dysfunction, clinicians should perform a detailed clinical history including the international prostate symptom score in males, physical examination with neurologic reflex, and rectal exam,

followed by laboratory work-up tests to assess renal function (serum creatinine), infections (urine exam), and clinical chemistry. Urodynamic evaluation is an essential component of examination. Although not indicated in all cases, includes cystometrogram, simultaneous studies of flow and pressure, sphincter electromyography and post-void residue measurement [34]. Diabetic women have significantly higher nocturia scores in lower urinary tract symptom questionnaires, with weaker urinary streams, reduced voided volumes, increased residual urine volumes, and lower maximal flow rates by uroflowmetry [46].

Treatment

The first step in the management of any type of diabetes complications is blood glucose control. Treatment for diabetic cystopathy depends on the severity of symptoms, but in early stages, it is basically conservative, and in case of complications, they should be treated accordingly [52]. In patients complaining of urgency, different types of first-line therapy are available, in order to control the hyperactivity of the detrusor, including oral muscarinic drugs and more uroselective anticholinergics with less adverse effects (oxybutynin, tolterodine, darifenacin, or solifenacin). Infiltration of the detrusor muscle with botulinum toxin has proven to diminish urgency incontinence. A surgical approach could be offered in severe cases of urgency incontinence not resolved with muscarinic selective anticholinergics, which includes bladder denervation, myomectomy, and bladder augmentation with ileal cystoplasty. All of them are associated with the risk of increasing post-void volume, urinary tract infection, kidney damage, and stone formation [52].

In males with added bladder outlet obstruction associated with prostate enlargement, initial treatment includes the use of alpha-blockers such as terazosin, tamsulosin, and alfuzosin. In advanced stages, transurethral resection of the prostate could be considered. A recently approved β3 adrenergic agonist (mirabegron) which increases the urine storage capacity, through direct detrusor smooth muscle relaxation, can be used to provide a rapid relief of symptoms [1, 17].

In cases of failure of bladder emptying, frequent clean intermittent catheterization is the best option to avoid the permanent use of indwelling catheters, because of the risk of increased infection rate, lower urinary tract lithiasis, and epidermoid bladder carcinoma [25]. In patients with urinary urge incontinence as the main symptom, anticholinergics, schedule voiding, and Kegel exercises to strengthen pelvic floor muscles may improve the quality of life.

Benign Prostatic Hyperplasia (BPH) and Urethral Obstruction

Benign prostatic hyperplasia (BPH) is an age-related phenomenon that affects up to 50% of men aged 60–69 years and almost 90% at age 90 [69]. DM is frequently associated with BPH due to the same age of incidence [6]. BPH has been largely associated with metabolic disorders including diabetes, metabolic syndrome, obesity, and hypertension. Preclinical and clinical studies have shown that increased plasma insulin levels are positive independent predictors of BPH, as well as high fasting glucose level and hyperlipidemia; all of them have shown a positive correlation to the progression of BPH [18, 19, 31].

Pathophysiology

Several theories have been proposed in the pathogenesis of BPH. The most convincing however is that prolonged chronic ischemia and repeated ischemia-reperfusion injury in the bladder could generate oxidative stress, which increases sympathetic nerve activity and vascular damage; further hypoxia of the bladder and prostate; and abnormal cell proliferation, in addition to an increase of lower urinary tract symptoms [69]. Endothelial dysfunction and nitric oxide (NO) deficiency are among the most important factors in the development of diabetic complications, affecting the lower urinary tract as well. Relaxation of the urethral sphincter is partially affected by NO, which in turn causes outflow obstruction and hyperexcitability of afferent neurons associated with progression of diabetes [72]. All these factors, in addition to the increased risk of overactive bladder in diabetic patients, are closely related to peripheral nerve irritation [75]. Another possible explanation for the presence of BPH in diabetic patients involves insulin-like growth factor (IGF). Beta cells of patients with type 2 diabetes secrete higher concentrations of insulin; the resulting hyperinsulinemia stimulates IGF synthesis. Activation of the prostate IGF receptors may also cause prostate growth [44, 74] which could be explained because of homology of insulin and IGF receptors [73] and cross-activity to insulin action [29, 50].

The pathogenesis of BPH is multifactorial and characterized by basal cell hypertrophy, secretory alterations of laminal cells, infiltration of lymphocytes with production of pro-inflammatory cytokines, stromal proliferation, diminished apoptosis, trans-differentiation and extracellular matrix production, abnormal autonomous innervation, and modification of the neuroendocrine cell function among others [69]. Disturbances in fatty acid metabolism are also influential in the progression of BPH, including inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2′-deoxyguanosine, and increased androgen synthesis [68].

Clinical Manifestations

Initially, patients with BPH complain of symptoms of LUTS (which already mentioned includes nocturia, frequency, urgency, weakened stream, hesitancy, intermittency, straining, and a sense of incomplete emptying) [27]. Progressive evolution toward complications in the urinary tract is more

important than symptoms related to micturition. They are significant and include bleeding, lithiasis, renal insufficiency, and infections [54], but the most serious and painful manifestation is acute urinary retention, the inability to urinate, characterized by intense pain in the pelvis [41].

Diagnosis

Evaluation of BPH in diabetic patients includes a detailed medical history, including LUTS questions, severity, and influence in their quality of life. The American Urological Association Symptoms Index (AUA-SI) is a questionnaire that allows physicians to quantify symptoms at diagnosis and over time in response to treatment. Digital rectal examination should be included in the physical examination. PSA (prostate-specific antigen), urinalysis, and frequency/volume chart may be filled as well as uroflowmetry, post-void residual ultrasound, and renal ultrasound in order to diagnose complications [27].

Treatment

To avoid complications, effective and conservative drug treatment for BPH is currently available. Patients with a small prostate are routinely treated with alpha-1 blocker monotherapy as first-line therapy, either with nonselective blockers such as doxazosin and terazosin or uroselective blockers like tamsulosin, alfuzosin, and silodosin. All of them have similar effectiveness but diverse side effect profiles. Characteristic side effects include postural hypotension, dizziness, rhinitis, asthenia, sexual dysfunction, and abnormal ejaculation. Storage and voiding symptoms improve briefly after initiation of treatment. Alpha-1 blockers do not prevent BPH progression [54]. For that reason, prostate volume and symptom progression should be monitored during the follow-up of the patient [27, 56].

In patients with a small prostate associated with voiding symptoms, the diagnosis of overactive bladder should be considered and treated as previously mentioned with anticholinergics, keeping in mind the need to monitor by dynamic bladder ultrasound the possibility of urinary retention, even though the risk is low.

In patients with enlarged prostate (over 30–40gr), the use of alpha-1 blockers in combination with an alpha 5 reductase inhibitor (finasteride or dutasteride) that blocks the conversion of dihydrotestosterone from testosterone is highly recommended, in order to diminish the prostate volume at long term with a faster effect on the relaxation of the bladder neck. In case of failure with all these therapies, the surgical approach is the next option. Transurethral resection of the prostate is the gold standard, but newer techniques such as bipolar resection and the use of laser vaporization, botox infiltration, cryotherapy, and high-intensity focused ultrasound among others, represent less invasive approaches than open adenomectomy [41, 56].

Sexual Dysfunction

Men and women with diabetes are affected by sexual dysfunctions, which are defined as the inability to achieve or maintain an adequate sexual response to complete a sexual encounter or intercourse resulting in a satisfactory orgasmic sensation. Sexual dysfunctions include disorders of libido, ejaculatory problems, orgasmic abnormalities, and erectile dysfunction. The reported prevalence of sexual dysfunction in men with type 2 diabetes is up to 46%. Sexual dysfunction in women is harder to diagnose, but it has been proposed that its prevalence in type 1 diabetes is 71% and 42% in females with type 2 diabetes [28, 61].

Almost half of non-sexually active men and women with type 2 diabetes report that their sexual life does not fulfill their sexual needs, suggesting that they are more concerned and even more distressed than sexually active patients. Commonly women argue that lack of sexual activity is related to a number of reasons, including lack of interest, physical problems that make it difficult or unpleasant, absence of partner, or having a partner with physical limitations [5].

Sexual dysfunctions involve a group of alterations that affect significantly the quality of life of these patients and include reduced desire, decreased arousal, orgasmic abnormalities, and painful intercourse [26].

Leading risk factors that further affect diabetic men and women include age, length of diabetes [5], co-medications, obstetric history, neurogenic and vascular complications, and infections among others.

Erectile Dysfunction (ED)

It is defined as a long-term, persistent inability to achieve or maintain an adequate rigid erection in order to have a satisfactory sexual encounter, and it is the third most frequent complication of diabetes and considered as one of the most significant complains affecting quality of life [48]. Manifestations usually appear after 10–12 years after the onset of diabetes, because of diabetic endothelial and neural damage associated with persistent high serum glucose levels [71].

ED affects approximately 18 million men in the United States, with an estimated prevalence of 35–90% in patients with diabetes [53]. Diabetic male patients generally have a greater prevalence and an earlier onset of erectile dysfunction than men without diabetes. Erectile dysfunction in diabetics is directly associated with poor glycemic control as well as greater duration and severity of diabetes [35]. Moreover, it has been demonstrated that ED is an early sign of cardiovascular events, particularly coronary heart disease. Prevention of cardiovascular disease through screening and management of cardiovascular risk factors in men with ED is very important [53].

Pathophysiology

Men with erectile dysfunction have diminished vasodilating responses causing less relaxation of the vascular smooth muscle tissue, due to deficient production of NO (nitrate oxide) in non-adrenergic, non-cholinergic neurons and in the endothelium [58]. These abnormalities are associated with important accumulation of advanced glycation products [15] and altered expression of arginase, a competitor of the NO synthase for its substrate L-arginine [8, 66]. All of these abnormalities cause a tendency toward vasoconstriction, such as that caused by phenylephrine and endothelin-1, resulting in lack of vasodilatation and inadequate penile erection.

Numerous mechanisms play important roles in the pathophysiology of erectile dysfunction in diabetic males; one of them is the polyol pathway, which forms sorbitol, by action of the enzyme aldose reductase. Sorbitol accumulates inside the cells, causing diminished myoinositol levels (a precursor of the phosphatidylinositol), required for the adequate functioning of the Na-K ATPase pump. Increased sorbitol concentrations additionally produce progressive peripheral nerve damage [59].

Regarding vascular component, endothelial damage is a central issue in ED, because in comparison with healthy males, diabetic male patients have a diminished arterial inflow, which has been observed microscopically with reduced diameter and deficient morphology of the vascular wall [37]. Contraction of cavernosal smooth muscle cells is also affected by hyperglycemia, which results in an increased forced response to vasoconstrictors. This could be partially explained because of sensitization in protein kinase C and Rho A-Rho kinase Ca2+ pathways, which may cause a tendency toward a flaccid stage and modify the responses to NO [21]. All of these mechanisms are further compromised by other factors that impact erectile function including apoptosis or atrophy of the cavernous smooth muscle, due to diminished expression of blc2, intracellular release of Ca2+, increased connective tissue proliferation due to tumor growth factor beta causing fibrosis and a deficient response to NO in the cavernous and sinusoidal artery, with a decrease in neuronal and endothelial levels of NO synthetase. In brief, there are several components that take place in the endothelial and neural damage in the periphery and central nervous system, which globally impact on ED in patients with DM.

Diagnosis

The International Index for Erectile Function Questionnaire helps to determine the degree of erectile dysfunction and to evaluate the progression or response to medical treatment. In certain cases, in which a more precise evaluation of vascular flows is needed, an echo-Doppler could be performed to determine cavernous artery flux and morphology. In selected cases, other studies to determine the degree of damage of myelinated pudendal somatosensory fibers and unmyelinated fibers can be done. Additional studies include assessment of nocturnal penile tumescence and electrostimulation. Most of these studies, however, are more commonly used in research protocols than in everyday clinical practice [24].

Treatment

Approximately 20% of patients with ED received pharmacological treatment; for that reason, clinicians should broadly evaluate sexuality among DM patients, trying to improve the sexual activity of patients and consequently their quality of life [5].

The first line of treatment are oral medications (phosphodiesterase 5 inhibitors), followed by intracavernosal injection (alprostadil), and finally penile prosthesis.

The daily use of phosphodiesterase 5 inhibitors can improve not only sexual function but also diminishes urinary tract symptoms associated with prostate enlargement. Meta-analysis has confirmed that phosphodiesterase 5 inhibitors are effective treatments of ED in patients with diabetes [4].

Sildenafil citrate, tadalafil, udenafil, and vardenafil hydrochloride are the oral agents for the treatment of erectile dysfunction. They all share the same mechanism of action, which involves the hydrolysis of guanosine monophosphate to guanosine 5′-monophosphate, diminishing it, causing an increase in the relaxation of the cavernosal smooth muscle mediated by NO, increasing the blood flow into the corpus cavernosum, and causing penile erection [9].

Common side effects of phosphodiesterase 5 inhibitors are headache, dyspepsia, bluish eye sight, and facial flushing; lumbar musculoskeletal pain has been found in patients receiving tadalafil and mirodenafil [4].

Vacuum erection devices cause blood flow to be directed into the penis, and when a satisfactory erection is obtained, a compressive device is applied at the base of the penis in order to prevent blood return and lose the erection. Side effects include cold penis due to non-circulating blood, loss or diminished sensation due to nerve compression, and the uncomfortable process to obtain the erection using the device [49]. External support devices that hold the flaccid penis to allow penetration have been designed, but the use of these instruments has not gained acceptance among patients and their partners.

Other medical options are intraurethral suppositories of prostaglandin E-1 which are injected into the urethra. In men with diabetes, their reported efficiency rate to achieve satisfactory intercourse is 60%, although in clinical practice they have not proved to be as effective [30, 43]. Injections of prostaglandin E-1 directly into the corpus cavernosum have a direct effect on blood vessels, causing immediate penile erections, with a reported response rate above 83% [42]. Main limitations include the need of injection prior to the sexual encounter, its impact on the spontaneity of sexual

intercourse, and adverse effects including penile pain, hematomas, infection, fibrosis and priapism, and prolonged and painful erections [62].

Patients not responding to medical therapy and unsatisfied with side effects or patients who prefer a permanent solution should consider a penile prosthesis implant (PPI). PPI improves flaccidity and rigidity and male satisfaction and correlates positively with satisfaction of the sexual partner. The rate of complications related to penile implantation is lower than 5%; they may be catastrophic, however, and include misplacement, migration, perforation, and a low risk of infection (less than 1.8%) using antibiotic prophylaxis, antibiotic impregnation, or hydrophobic-coated prosthesis [3].

Urinary Tract Infections

The worldwide prevalence of urinary tract infections (UTI) is around 150 million persons per year [67]. DM patients have a higher incidence of infections in general, and UTI are not the exception. The variety of UTI patients with diabetes ranges from asymptomatic bacteriuria to cystitis, pyelonephritis, renal abscess, and xanthogranulomatous pyelonephritis, to severe urosepsis [60]. DM is also associated with severe cutaneous infections of the genitals such as Fournier's gangrene. Asymptomatic bacteriuria is more prevalent in women, due to the anatomical length of the urethra, and it is closer to the warm, moist, vulvar, and perianal areas that are commonly colonized by enteric bacteria [60]. DM female patients frequently suffer bacterial cystitis with higher prevalence of both asymptomatic bacteriuria and symptomatic UTI added to recurrent complications, compared to healthy women [67].

Bacterial cystitis is frequently suffered by diabetic patients; it is more common in women than in men, especially in those with type 2 DM. Diabetic women have a higher prevalence of asymptomatic bacteriuria than healthy women, and they have a greater tendency for developing symptomatic UTI and recurrent complications with higher incidence of more serious complications [32, 33].

Type 2 DM is more than a risk factor for community-acquired UTI and is a high predisposition for healthcare-associated UTI, such as catheter-associated UTI, post-renal transplant recurrent UTI, and catheter-associated UTI [60]. Hospitalization due to pyelonephritis occurs more frequently in diabetic patients, and they are at higher risk of developing acute pyelonephritis, which could progress to renal abscess, pyelitis, or emphysematous cystitis or pyelonephritis and bacteriemia [60, 70].

Pathophysiology

The increased frequency of UTI in patients with diabetes might be associated with nerve damage caused by hyperglycemia, affecting the capacity of bladder to sense the presence of urine and leading to stagnation of urine for a long time or inadequate bladder emptying due to ineffective detrusor contraction, increasing the probability of infections [67]. In addition, higher renal parenchymal glucose levels create a favorable atmosphere for multiplication of many microorganisms [60].

DM results in abnormalities in the host immune defense system that may result in higher risk of developing infection. Immunologic impairments such as defective migration and phagocytes alterations of chemotaxis in polymorphonuclear leukocytes are common in DM patients [22]. Additionally, certain cytokines such as IL-6, IL-8, and other pro-inflammatory cytokines are diminished in the urine in comparison to healthy women [14, 60]. Diminished neutrophil responses and lower levels of cytokines and leukocytes facilitate adhesion of microorganisms to uroepithelial cells and the development of infections [40].

Clinical Manifestations

UTI in DM patients can be the origin of severe complications that can end up in sepsis, organ failure, and death. Therefore, it is important to be vigilant of the usual clinical manifestations such as urinary urgency, frequency, bad urine odor, pain, dysuria, tenesmus, incomplete emptying, and incontinence for lower UTI and costovertebral angle pain or tenderness, fever, and chills for upper UTI [60].

Premenopausal and postmenopausal women have a double risk of developing the UTI [10]. Another risk factor is sexual intercourse, which is the most important risk factor in patients with type 1 diabetes [32, 33].

Diagnosis

Frequent and early screening for UTI should be performed in DM patients with suggestive symptoms, in order to establish the appropriate early treatment and to avoid complications.

As soon as the clinical diagnosis of UTI is suspected, a midstream urine sample must be examined, looking for the presence of leukocytes (more than 10 leukocytes/mm^3) or a positive dipstick leukocyte esterase test to detect pyuria. Microscopic or macroscopic hematuria is sometimes observed [60], associated with positive nitrites and the presence of bacteriuria.

Before the initiation of antimicrobial treatment, a urine culture should be obtained from voided, clean-catch midstream urine. In case this method is impossible, a culture through a sterile urinary catheter should be done [60]. Despite the fact that *Escherichia coli* is the most frequent bacteria in patients with urinary tract infections, unusual, multidrug-resistant and aggressive pathogens are more prevalent in DM patients, including *Klebsiella*, gram-negative rods, enterococci, group B streptococci, *Pseudomonas*, and *Proteus mirabilis* [63]. Type 2 DM is a risk factor for fungal UTI, such as candida; these patients are more predisposed to be infected by resistant pathogens, including extended spectrum β-lactamase-positive *Enterobacteriaceae*, fluoroquinolone-resistant uro-

pathogens, carbapenem-resistant *Enterobacteriaceae*, and vancomycin-resistant *Enterococci* [60].

Treatment

Glycemic control is helpful in the control of UTI [67], and treatment of asymptomatic bacteriuria is not indicated [60]. The use of cotrimoxazole for 3 days is recommended for the treatment of uncomplicated cystitis as first-line therapy [39]. Strategies to prevent recurrent UTI include postcoital antibiotics or prophylactic antimicrobials, taken on a regular basis at bedtime. The use of trimethoprim, cotrimoxazole, or nitrofurantoin is considered as the standard regimen of antibiotic therapy [36].

Conclusions

Patients with diabetes are highly susceptible to urologic complications. They may be serious and life-threatening and affect quality of life. It is important to take into account these comorbidities in the management of diabetes and to understand their pathogenesis to prevent systemic dissemination. Many patients with diabetes accept these comorbidities are part of their disease, but clinicians should be aware, interrogate, and screen for these complications in order to indicate the adequate treatment.

Multiple-Choice Questions

1. Urologic complications in people with diabetes are associated with:
   (a) Nerve function disturbances
   (b) Loss of innervations of neuromuscular terminals
   (c) Abnormal immune responses
   (d) Altered sympathetic/parasympathetic innervations
   (e) All of the above
2. Peripheral accumulations of fat in the abdominal region of DM patients have been associated with an increased risk of urologic complications including:
   (a) Urinary incontinence
   (b) Erectile dysfunction
   (c) Benign prostatic hyperplasia
   (d) Urinary tract infections
   (e) Cancer
3. Diabetic cystopathy is characterized by:
   (a) Urinary incontinence
   (b) Increased post voiding residual volume
   (c) Urinary tract infection
   (d) All of the above
   (e) None of the above
4. Bladder symptoms of diabetic cystopathy include:
   (a) Pollakiuria
   (b) Decreasing caliber and strength of the voiding flow
   (c) Terminal dribbling
   (d) Urgency incontinence
   (e) High post-void residual urine
5. Infiltration of the detrusor muscle can be achieved with:
   (a) Oxybutynin
   (b) Solifenacin
   (c) Botulinum toxin
   (d) Darifenacin
   (e) Tolterodine
6. Positive predictive predictors of benign prostatic hyperplasia:
   (a) Urinary tract infection
   (b) Plasma insulin levels
   (c) Dysuria
   (d) Urinary urgency
   (e) Fasting blood glucose
7. Patients with benign prostatic hypertrophy and enlarged prostate should be treated with:
   (a) Non-selective alpha-1 blockers
   (b) Selective alpha-1 blockers
   (c) Alpha reductase inhibitors
   (d) Alpha-1 blockers combined with 5 alpha reductase inhibitors
   (e) Surgical management is the only option
8. The reported prevalence of sexual dysfunction in men with type 2 diabetes:
   (a) 18%
   (b) 37%
   (c) 46%
   (d) 53%
   (e) 71%
9. The reported prevalence of sexual dysfunction in women with type 1 diabetes is:
   (a) 18%
   (b) 37%
   (c) 46%
   (d) 53%
   (e) 71%
10. Erectile dysfunction:
    (a) Is a minor complain of men with diabetes
    (b) Has not been quantified
    (c) Is usually present at diagnosis
    (d) Is the third most common chronic complication and the most significantly affecting quality of life
    (e) Is common but less relevant regarding quality of life

Correct Answers

1. (e) All of the above
2. (a–e)
3. (a–c)
4. (a, d)
5. (c) Botulinum toxin

6. (d) Urinary urgency
7. (d) Alpha-1 blockers combined with 5 alpha reductase inhibitors
8. (c) 46%
9. (e) 71%
10. (d) Is the third most common chronic complication and the most significantly affecting quality of life

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